REMARKS

Claims 4, 15-22, 32-36, and 46-84 stand cancelled by this amendment. Claims 15-21, 32-35, and 46-84 are directed to subject matter not elected in response to a restriction requirement. Claim 4 is cancelled solely in order to expedite prosecution of the pending application to issue. Claims 22 and 36 are cancelled as duplicative in view of the amendments to limiting claims 1 and 28 to antibody antagonists.

Support for the amendment to the title may be found, for example, in the specification at page 6, lines 11-29 and on page 7, lines 1-11. Support for the amendments to claims 1, 23, 28, 37 and 40 may be found, for example, in Figure 2 and in the specification at page 7, lines 12-13 and at page 10, line 8. No new matter is added by way of the amendments.

The Examiner states (page 2, lines 19-22) "Claims 1-14, 22-27, 28-31 and 36-45, as they read on the methods for controlling excessive proliferation of smooth muscle an [sic] method for treating stenosis comprising administering an effective amount of an antagonist of a native ErbB4 receptor, wherein antagonist is an antibody are under consideration in the instant application."

Applicants respectfully disagree with this characterization of the pending claims, and note, for example, that claims 1-14 and 22-27 recite methods for controlling excessive proliferation *or migration* of smooth muscle cells utilizing an antagonist of a native mammalian ErbB4 receptor.

Claim Rejections under 35 U.S.C. 112, first paragraph

Claims 1-14, 22-27, 28-31 and 36-45 stand rejected under 35 USC § 112, first paragraph, the Examiner stating that "[t]he specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation." The Examiner suggests that these claims do not satisfy the requirements of 35 USC § 112, first paragraph for alleged lack of animal testing (*e.g.,* point 9, page 4, paragraph 5 to page 5, paragraph 1), for alleged difficulty in establishing that the antibodies would

prevent disease (point 9, page 5, paragraph 3 continuing onto page 6), and for alleged lack of guidance about screening and testing protocols (point 9, page 6, paragraph 2). The Examiner also suggests that treatment protocols, in the absence of *in vivo* clinical data, may be unpredictable (point 9, page 5, paragraph 2). Applicants respectfully traverse the rejections of claims 1-14, 22-27, 28-31 and 36-45.

The Examiner suggests that the specification might not be enabling due to lack of animal testing data. However, a patent specification is not required to include disclosure regarding animal testing. Referring to the use of testing to demonstrate the usefulness of compounds, the Federal Circuit stated "test results need not absolutely prove that the compound is pharmacologically active. ... there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior." (Fujikawa v. Watanasin, 93 F.3d 1559, 1564 (Fed. Cir. 1996). Quoting (Cross v. Iizuka, 753 F.2d 1040, Fed. Cir. 1985): "evidence of *in vitro* testing could adequately establish practical utility" the Federal Circuit then said "we agree with the Board that this *in vitro* utility is sufficient ..." (Fujikawa v. Watanasin, 93 F.3d 1559, 1565 (Fed. Cir. 1996).

In vitro tests are widely used to identify pharmacologically active compounds and to develop treatments for diseases. For example, Topol et al. report *in vitro* results along with their clinical results showing efficacy of an antibody that binds to the $\alpha_{IIB}\beta_3$ ($\alpha_v\beta_3$) integrin (found on platelets) and to vitronectin (found on smooth muscle) in treating vascular stenosis. Accordingly, applicants respectfully submit that there is thus no proper basis for the rejection of claims 1-14, 22-27, 28-31 and 36-45 for lack of disclosure related to animal testing.

The Examiner has also suggested that there might be difficulty in establishing that the antibodies would prevent excessive proliferation or prevent stenosis. Applicants note that Topol et al. state that abciximab, an antibody, binds to the vitronectin receptor, and that *in vitro* experiments have shown that vitronectin blockade

strongly inhibits smooth muscle cell migration. Topol et al. further disclose that the antibody abciximab is effective in reducing mortality, myocardial infarction, and the need for revascularization in human coronary angioplasty patients followed for several years after treatment (e.g., Fig. 2, Topol et al.). Thus, in a routine study of abciximab, the normal follow-up disclosed the prevention of new coronary atherosclerotic events in patients studied who received the treatment (Topol et al., page 482, column 2, lines 17-19).

Applicants note that the specification clearly discloses that the antagonists used in practicing the invention are effective (see, *e.g.,* Figures 5 and 6) and discloses methods for practicing the invention as claimed (*e.g.,* page 55, line 15 – page 62, line 11). Thus, from at least the disclosure provided by the specification and by published research reports, one of ordinary skill in the art would reasonably believe that the ErbB4 antibody antagonists claimed in the present application would be effective in preventing disease.

Applicants respectfully submit that further disclosure is not required. As stated at 2164.06 (c) of the MPEP "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." citing several cases, including *In re Brana*, 51 F.2d 1560, 1566 (Fed. Cir. 1993).

The Examiner suggests that the pending claims may not be enabling under 35 U.S.C. § 112, first paragraph for alleged lack of guidance about screening and testing protocols. Applicants respectfully draw the Examiner's attention, for example, to pages 62, line 12 to page 65, line 10 (disclosing methods for identification of molecules that affect smooth muscle proliferation or migration) and to page 67, line 17 to page 69, line 3 (disclosing methods and results of experiments measuring the effects of ErbB4 antagonists), where substantial disclosure on this topic is provided. Moreover, as discussed above, screening and testing procedures are known in the art (see, *e.g.,* the

patient follow-up procedures in Topol et al. (the results of which are shown, *e.g.,* in Fig. 2) demonstrating prevention of new coronary atherosclerotic events).

Thus, since methods are disclosed in the specification, and screening and testing protocols are known in the art, no undue experimentation is required to practice the invention. As the Federal Circuit stated in Johns Hopkins University v. Cellpro, Inc., "routine experimentation does not constitute undue experimentation ..." (152 F.3d 1342, 47 USPQ2d 1705 (Fed. Cir. 1998)).

The Examiner suggests that Menges et al. "teach that benefit of immunosuppressive therapy in the prevention of recurrent stenosis is not established" and goes on to suggest that undue experimentation would be necessary to demonstrate the efficacy of the present invention. However, Menges et al. do not discuss antibody therapy directed at ErbB4 receptors, but instead were referring to steroid therapy (*e.g.,* page 483, col. 1l, lines 15-19). Thus, Menges et al. do not suggest that the present invention, directed at ErbB4 receptors, might not have efficacy. Moreover, Topol et al. do demonstrate efficacy of an antibody treatment, showing sustained benefit for up to 2.5 years follow up (p. 482, column 2, lines 14-20), so that one of ordinary skill in the art would not find that undue experimentation was necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

The Examiner cites Topol et al. for the propositions that many agents have failed to reduce stenosis or restenosis or to improve long-term clinical outcomes. However, as noted by the Examiner, Topol et al. itself reports the success of an agent in reducing stenosis or restenoisis: $\alpha_v\beta_3$ integrin blockade strongly inhibits smooth muscle cell migration: (page 482, column 3, lines 38-42). Topol et al. cite this *in vitro* finding in their explanation of the observed clinical efficacy of abciximab. Topol et al. provide an example of an antibody antagonist that is effective in cell culture and whose clinical efficacy, indicated by the *in vitro* experiments, is confirmed by clinical findings in human patients and thus providing an art-recognized example of a correlation between *in vitro* data and *in vivo* data. Thus, Applicants respectfully submit that Topol demonstrates

that antibodies directed to smooth muscle cells can inhibit smooth muscle cell proliferation, can reduce stenosis or restenosis, and can improve long-term clinical outcomes.

Applicants thus submit that claims 1-14, 22-27, 28-31 and 36-45 are fully enabled in the specification, and that the rejections of these claims under 35 U.S.C. § 112, first paragraph are overcome.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 1-14, 22-27, 28-31 and 36-45 stand rejected under 35 USC § 112, second paragraph as allegedly being indefinite, the Examiner objecting to the use of the term "ErbB4 receptor" as the sole means of identifying that receptor.

Applicants respectfully submit that the term "ErbB4 receptor" recited in the claims as originally filed provides sufficient and definite identification for one of ordinary skill in the art. However, in order to expedite the prosecution of the present application to issue, claims 1, 23, 28, and 37 have been amended to recite SEQ ID NO.: 2 to provide additional identification of the ErbB4 receptor to which the antagonists of the claimed methods are directed.

Claim Rejections - 35 USC § 103(a)

Claims 1-3, 5-14, 22-31 and 36-45 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Plowman et al. (U.S. Patent 5,811,098) in view of Krymskaya et al. (Am. J. Physiol. 276:L246-L255 (1999)) or Godowski et al. (WO 99/02681) and further in view of a "known fact disclosed in the specification at page 5, lines 7-25." Applicants traverse this rejection, and respectfully submit that claims 1-3, 5-14, 22-31 and 36-45 are not obvious over the cited combination of references.

In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or

suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that motivation or suggestion to combine the references is lacking, that there would be no reasonable expectation of success based on these references, and that the references cited by the Examiner fail to provide all the elements of the claimed invention.

Plowman is presented by the Examiner to provide an amino acid sequence of the HER4 receptor that is identical to the ErbB4 receptor of the present application. As noted by the Examiner, Plowman is directed to cancer cells, and does not teach methods directed to smooth muscle cells.

The "known fact disclosed in the specification at page 5, lines 7-25" is apparently that excessive proliferation of smooth muscle cells is involved with vascular stenosis, restenosis, and hypertension.

Krymskaya et al. is presented by the Examiner to show the presence of ErbB4 receptors on smooth muscle cells, and suggests that the ErbB4 receptor plays "a pivotal role in the regulation of smooth muscle cells ..." However, Applicants respectfully direct the Examiner's attention to Krymskaya et al., page L252, column 2, lines 7-9: "Although all EGFR family members are expressed in quiescent HASM [human airway smooth muscle] cells, ErbB-3 and ErbB-4 are functionally inactive." Applicants further note page L248, column 2, lines 37-39: "ErbB-3 and ErbB-4 in EGF-stimulated cells did not appear to be activated." Thus, Krymskaya et al. teach that ErbB4 receptors do NOT play a role in smooth muscle cell proliferation of human airway smooth muscle cells. Krynskaya et al. thus teach that interaction with an ErbB-4 receptor would be ineffective at affecting smooth muscle cell proliferation.

Krymskaya et al. thus provides no teaching that one could control or inhibit smooth muscle cell proliferation, or affect stenosis or restenosis, by treatment with an

antagonist to an ErbB4 receptor. Teaching that ErbB-4 receptors are functionally inactive on the smooth muscle cells investigated, Krymskaya et al. does not provide any motivation to combine with any other reference to control or inhibit smooth muscle cell proliferation, or affect stenosis or restenosis, by treatment with an antagonist to an ErbB4 receptor.

WO 99/02681 is presented by the Examiner to show that ErbB4 receptors are present on smooth muscle cells, "and that blocking signal transduction pathway mediated through this receptor can effect mitotic activity." WO 99/02681 provides an example of enhanced neuronal cell proliferation with treatment of NRG3 (an ErbB4 ligand; Example 6) and states that NRG3 "may be used to treat diseases caused by skeletal or smooth muscle wasting" (page 43, lines 11-12). However, WO 99/02681 nowhere suggests that antagonists to ErbB4 receptors might be useful to control smooth muscle proliferation. Accordingly, WO 99/02681 provides no teaching that would render obvious the claimed invention, nor any suggestion that it be combined with other references to provide the claimed invention.

"Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). Applicants respectfully submit that WO 99/02681 provides no suggestion or motivation to combine with any other reference or with knowledge available to one of ordinary skill in the art to provide ErbB-4 antagonists to control or inhibit smooth muscle cell proliferation, or to treat stenosis or restenosis, and that its use in a combination of references to provide such a teaching must be the result of impermissible hindsight.

Moreover, even if the cited references were combined, elements of the claimed invention remain lacking. For example, the cited references lack any teaching that antagonists to ErbB4 receptors would be effective to reduce smooth muscle proliferation. As discussed above, Krymskaya et al. teach that ErbB4 receptors are

inactive, WO 99/02681 contains no disclosure regarding antagonizing ErbB4 receptors to reduce smooth muscle cell proliferation, and Plowman "does not teach a method of controlling excessive proliferation ..." (Page 7, last two lines). Thus, the cited references, even if combined, lack at least the teachings that antagonists to ErbB4 receptors are effective to control excessive proliferation or migration of smooth muscle cells and to treat stenosis or restenosis in a mammal. Accordingly, Applicants respectfully submit that the rejections of claims 1-3, 4-14, 22-31 and 36-45 under 35 U.S.C. § 103(a).

CONCLUSIONS

Applicants believe all rejections to be overcome as discussed above, and respectfully request the reconsideration and allowance of all pending claims. All claims being believed to be in *prima facie* condition for allowance, an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing attorney's docket no. **39766-0072 A2**.

Respectfully submitted,

Dated: May 20, 2003

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